Motor fluctuations and psychological distress in Parkinson's disease
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Abstract

Objectives: Off periods in Parkinson's disease (PD) are associated with a worsening of non-motor symptoms and acute psychological distress. The relationship between motor fluctuations and episodic distress in naturalistic settings remains unclear, particularly the role of individual psychological factors. This study aimed to identify those factors through real-life, real-time assessment using Ecological Momentary Assessment (EMA).

Methods: Twenty participants (seven female) completed multiple brief prompted surveys over a 7-day period assessing current motor and medication state, social situation, episodic distress, and cognitive processes (rumination, symptom focus, and worry). Baseline depression and anxiety were measured using validated questionnaires, as were positive and negative beliefs and attitudes (metacognitions) regarding cognitive processes. The feasibility of EMA via smartphones was assessed at the end of the study.

Results: Four-hundred and ninety-six complete datasets were collected across participants. Generalized linear mixed model regression analyses showed that episodic distress was predicted by a combination of cognitive processes [F (1, 483) = 41.14, p < .001], momentary motor state [F (3, 483) = 10.40, p < .001], time of day [F (1, 23) = 12.42, p = .002], and trait negative metacognitions [F (1, 6) = 7.21, p = .037)]. EMA was judged acceptable by the majority of participants.

Conclusions: Time of day, cognitive processes, and negative metacognitions predict episodic distress independent of motor state. This indicates potential targets for non-pharmacological interventions aimed at alleviating episodic distress in patients with motor fluctuations. EMA is a feasible methodology for PD research and potential tool for delivering such interventions.

Parkinson's Disease and Motor Fluctuations

Parkinson's disease (PD) is a common neurodegenerative condition, affecting around one in 100 people over 70 years of age in the UK (Pringsheim, Jette, Frolkis, & Steeves, 2014). In addition to motor symptoms, it is associated with a wide range of non-motor symptoms (NMS) including depression, anxiety, cognitive impairment, fatigue, sleep disturbance, autonomic dysfunction, and pain. NMS can predate motor symptoms, contributing an increasing burden with disease progression (Martinez-Martin et al., 2007) and having a greater negative impact on health-related quality of life than motor symptoms (Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011).

Dopamine replacement therapy (DRT) is linked to a range of complications with long-term use including motor fluctuations, ranging from akinetic-rigid hypodopaminergic 'off' periods/states, to phases of relatively good motor control ('on' periods/states) or hyperdopaminergic dyskinetic states (Bjornestad et al., 2016; Kostić, Marinković, Svetel, Stefanova, & Przedborski, 2002; Schrag & Quinn, 2000). Off periods are attributed to 'wearing off' (related to the time elapsed since the previous DRT dose), a 'delayed on' (when a DRT dose-effect occurs later than expected), or when a DRT dose has no effect (Lyons & Pahwa, 2011). In addition to increased motor symptom severity, off periods are also associated with an acute emergence or worsening of a range of NMS including autonomic symptoms, fatigue, pain, limb paresthesia, cognitive/concentration difficulties, low mood, and anxiety (Rizos et al., 2014; Storch et al., 2013).

Emotion in Parkinson's Disease

Anxiety and depression are frequently co-morbid in PD, with their etiology and maintenance likely due to underlying disease-specific pathophysiology and psychosocial factors common to other chronic health conditions (Schrag, Jahanshahi, & Quinn, 2001; Tang & Strafella, 2012; Veazey, Aki, Cook, Lai, & Kunik, 2005). Prevalence estimates of mood

disorders in PD are high: e.g., between 25% and 43% for anxiety disorders (Dissanayaka et al., 2010; Pontone et al., 2009), 17% for major depressive disorder, 22% for minor depression, 13% for dysthymia, and 35% for clinically significant sub-threshold depressive symptoms (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Some PD patients may suffer from a combination of anxiety and depressive symptoms that do not meet diagnostic criteria for a psychiatric disorder but have a significant impact on quality of life (Reiff et al., 2011; Santangelo et al., 2014; Schapira, Chaudhuri, & Jenner, 2017). While anxiety and depression refer to formal psychiatric disorders and their subsyndromal forms, the broader construct of 'psychological distress' is commonly used to describe a negative mixed emotional state and its physical concomitants. Distress may occur in a wide range of situations in the context of physical or psychological discomfort or threat often experienced by people living with chronic health conditions.

Greater levels of depression and particularly anxiety have been reported in patients who experience motor fluctuations compared to those who do not (e.g., Burn et al., 2012; Pontone et al., 2009). These mood states may span motor states, though there is compelling evidence of acutely elevated distress during off periods for many patients (Brown, Marsden, Quinn, & Wyke, 1984; Cantello, Gilli, Riccio, & Bergamasco, 1986; Leentjens et al., 2012; Menza, Sage, Marshall, Cody, & Duvoisin, 1990; Nissenbaum et al., 1987; Racette et al., 2002). However, these studies did not gather longitudinal and/or naturalistic data, tempering the strength of conclusions about the temporal relationship between mood and motor state. Furthermore, episodic distress may have a direct hypodopaminergic component (Martinez-Fernandez, Schmitt, Martinez-Martin, & Krack, 2016), as well as reflecting an emotional response to worsening motor and NMS.

However, acute episodic distress is not an inevitable feature of off periods. For example, it may be moderated by psychosocial factors, such as the nature of the interpersonal

relationships of people living with PD or exacerbated by a sense of embarrassment (Backer, 2000; Frazier, 2000). Specific cognitive processes may also play a key role in distress: e.g., a tendency to ruminate and engage in symptom focusing (Julien, Rimes, & Brown, 2016) have been incorporated into a recent cognitive model of anxiety and depression in PD (Egan, Laidlaw, & Starkstein, 2015). Rumination refers to a cognitive process characterized by repetitive thinking about abstract questions (e.g., "Why is this happening to me?") and symptom focusing to attentional focus on PD symptoms whether momentarily present or not.

The Self-Regulatory Executive Function (S-REF) model asserts that cognitive processes (such as rumination, symptom focus, and worry) are components of a Cognitive Attentional Syndrome (CAS), causing and maintaining psychological distress, and are fueled by the beliefs held about them, referred to as 'metacognitions' (Wells & Matthews, 1994, 1996). These beliefs can be conceptualized as 'thoughts-about-thoughts' that outline 'general plans for processing and coping' (Wells, 2002, 2009). Metacognitions are often categorized as positive (e.g., "If I focus on my symptoms, I can better control them.") or negative (e.g., "Once I focus on my symptoms, I find it impossible to pay attention to anything else."). In PD, metacognitions have been implicated in both general and episodic distress (Allott, Wells, Morrison, & Walker, 2005; Brown & Fernie, 2015; Fernie, Spada, Ray Chaudhuri, Klingelhoefer, & Brown, 2015).

Study Aims

Clinically, when effective control of motor fluctuations is limited, interventions are needed to reduce their psychological burden. Identifying psychosocial predictors of episodic distress, independent of motor state, may reveal novel targets for non-pharmacological interventions. The present study aimed to extend previous research, testing whether momentary motor state, the CAS, and metacognitions (Brown & Fernie, 2015; Fernie, Spada, et al., 2015) contribute to episodic distress (experienced by people with PD who have

developed motor fluctuations) using data gathered in naturalistic settings. The current study used Ecological Momentary Assessment (EMA), which has been successfully used previously in PD (Broen et al., 2016; van der Velden, Mulders, Drukker, Kuijf, & Leentjens, in press). EMA possesses several advantages relevant to the current study's aims. It is less vulnerable to retrospective recall biases than studies that employ self-report measures with cross-sectional designs. EMA gathers real-time, longitudinal quantitative data in a naturalistic setting.

The current study had two central objectives: examining the acceptability and feasibility of using EMA, and identifying factors associated with episodic distress (including those derived from the S-REF model), in a sample of people living with PD who have developed motor fluctuations. Capturing momentary changes in distress and motor state was vital to testing the current study's two hypotheses that operationalized the second objective: i.e., (1) there would be a reliable relationship between motor state and episodic distress, and (2) cognitive processes and metacognitions would significantly predict episodic distress when controlling for motor state.

Methods

Participants

Twenty participants (seven females; mean age = 60.8 years; range 48-79; *SD* = 9.3) were recruited from the Movement Disorders Service at a London Hospital (n = 18) and through web-adverts published by a patient advisory group (n = 2; Parkinson's UK). Eligibility criteria required participants: (1) had a clinical diagnosis of idiopathic PD, (2) were taking DRT, (3) self-reported experiencing off periods for at least 25% of their day (however, participants were not required to report elevated levels of episodic or general distress), (4) adequately comprehended the English language, (5) were able to use a touch screen on a smartphone, (6) did not have clinical evidence of dementia, and (7) were able to

provide informed consent. The Movement Disorders Service identified 19 eligible and interested individuals, all of whom provided consent to participate in the study. However, one individual later decided not to participate before contributing any data, after reflecting that adhering to the EMA schedule would be too demanding. The two participants recruited following Parkinson's UK were the first two individuals who contacted the research team. The study received ethical approval from the Dulwich Research Ethics Committee (14/LO/0714).

Measures and Procedure

Following consent, participants provided demographic and clinical information, including date of PD diagnosis, typical pattern of motor fluctuations, and medication regimen. Participants also completed three self-report measures assessing trait metacognitions and affect over the previous 2 or 4 weeks. The 17-item Metacognitions about Symptom Control Scale (MaSCS; Fernie, Maher-Edwards, Murphy, Nikcevic, & Spada, 2015) assessed both positive and negative metacognitions (PM and NM) about rumination and worry about symptoms and symptom focus. An earlier study tentatively reported a relationship between PM and NM with anxiety and depression in a sample of people with PD and distressing off periods (Fernie, Spada, et al., 2015). Higher scores on the MaSCS indicate stronger endorsement of PM and NM. Anxiety over the preceding 4 weeks was assessed using the 12-item Parkinson's Anxiety Scale (PAS; Leentjens et al., 2014), consisting of three subscales (persistent, episodic, and avoidance anxiety), and depressive symptoms over the past 2 weeks using the nine-item Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001). The PAS and PHQ-9 were used to characterize the sample but not in the subsequent modelling.

After completing the self-report measures, participants began a 7-day EMA data collection period. An EMA software application ('App') was built on the MovisensXS

platform (gathering encrypted data) for Android operating system (GmbH, 2015) and deployed on 'Google Nexus 5' smartphones (on which all telephony and data services had been disabled), provided by the research team for the study period. The App's design was informed by feedback from Parkinson's UK. It was programmed to produce four random auditory alerts per day, scheduled between 8am and 8pm (stratified into four, 3-hour windows). Following an alert, participants could choose to complete (or postpone, or dismiss, completion of) a brief survey. Also, participants could self-initiate a survey at any time. The context data gathered by EMA was structured and momentary time sampled.

Each survey consisted of seven items asking about their momentary motor state ('Motor', including on and off periods and transitional states: i.e., on-wearing-off and off-coming-on), the psychosocial context ('Company'), the interval between the survey time and the last DRT dose ('Medication'), level of episodic distress ('Distress'), and the extent which a participant was engaging in certain cognitive processes (see Supplementary Material 1). Episodic distress and cognitive process engagement was assessed using an ordinal, five-point response format. The hour of the day each individual survey was completed defined the variable 'Time'. How a survey was initiated (either participant-initiated or in response to a random alert) was used to create a dichotomous variable labelled 'Trigger'.

Before beginning the EMA data collection period, participants were taught how to use the smartphone and the App and provided with an instruction manual (paper copy) for reference. Also, participant could use the App to send messages to the research team, or could contact them by telephone or email, should they have had any questions or concerns about using the App (or about the study in general). Following the EMA data collection period, participants were debriefed and completed a questionnaire addressing the usability of the App.

Data Processing and Statistical Analysis Methods

All analyses were conducted using version 24 of SPSS (International Business Machines Corporation, 2017). Means, SD, ranges, and (following normality tests) non-parametric correlation analyses were calculated using all baseline self-report measures. Counts, medians, IQRs, ranges, and percentages were used to describe the characteristics of the EMA data in terms of momentary motor state and how completed surveys were triggered.

Detailed analysis of EMA data to test the study's hypotheses was achieved with generalized linear mixed regression modeling (GLMM). GLMMs allow both fixed and random effects to be specified as predictors for non-normally distributed and non-continuous dependent variables. Fixed effects are variables generalizable to a wider population while random effects are specific to the sample. Random effects model variation between participants, contributing to the control of individual differences. EMA produces longitudinal, real-time data. When analyzing data with these characteristics it is important that time is modelled. GLMMs can control for time by specifying it as a repeated measures effect, fixed effect, and/or as a random effect (i.e., a random slope describing relationships between time and the outcome variable for each participant).

The GLMMs built for the current study controlled for time by specifying it as a fixed effect (which modelled the relationship between the hour of day and episodic distress for the whole sample) and a random slope (modelling variation in how episodic distress changed over the course of a day for each participant). The GLMMs reported in the current study all used episodic distress as the dependent variable with multinomial distributions and a Probit link function (modelling the relationship between the independent variable and the dependent variable). The models employed robust estimation to 'handle violations of model assumptions' and Satterthwaite approximation. Random effects were modelled using a variance components covariance matrix.

The current study reports two GLMMS. The first model focused on the relationship between episodic distress with momentary motor state while the second the relationship between motor state and momentary cognitive process activation and metacognitions. The first model controlled for Time, Company, Medication, and Trigger. The second model was built from the first, controlling for significant predictors that had been found while excluding those nonsignificant. This exclusion strategy was employed to optimize the number of parameters needed to estimate the model, enhancing statistical power.

Results

Participant Characteristics and Baseline Self-Report Measures

All 20 participants had received a clinical diagnosis of PD and were taking DRT. The mean duration since the participants' PD diagnosis was 7.6 years (range 1 to 20 years; *SD* = 5.1). All participants self-reported experiencing motor fluctuations and spending a quarter of their days in an off state. Nineteen participants self-reported as British. All but three participants reported that English was their first language. All participants had attended formal education up until at least the age of 16 years, with four educated to university degree-level.

Table 1 shows the means, SD, and intercorrelations between the self-report measures assessed at baseline. NM (but not PM) positively and significantly correlated with total PAS and PHQ-9 scores. Twelve participants had significant anxiety based on the total PAS score (cut-off 13/14), with six showing significant persistent anxiety (cut-off 9/10), three significant episodic anxiety (cut-off 5/6), and nine significant avoidance anxiety (cut-off 4/5). On the PHQ-9, nine showed evidence of no, minimal, or mild depression (score < 10), six moderate depression (score 10-14), and five moderately severe depression (score 15-27).

Characteristics of Ecological Momentary Assessment Data

A total of 560 random alerts were produced by the smartphone App over the combined study periods for all participants, of which 50.2% generated completed EMA surveys. Four-hundred and ninety-eight completed surveys were generated, of which 43.6% were participant-initiated surveys. Table 2 shows the counts of completed surveys, stratified by Trigger and Motor. Five (25.0%) participants did not complete a survey during an off period, four (20.0%) when off-coming-on, and two (10.0%) when on-wearing-off. All participants completed surveys when on. Thirteen (65.0%) participants completed surveys in response to 50% or more of the random alerts, seven (35.0%) to 60% or more, and five (25.0%) to 70% or more. Of the 279 (49.8%) of the random alerts that were not responded to, 33 (11.8%) were actively dismissed, 136 (48.7%) ignored, six (2.2%) incomplete, and for 104 (37.3%) no data was recorded. The latter likely indicated the smartphone was switched off or out of battery. The mean recorded duration taken to complete a survey was 68.5 seconds (range 13-606 seconds; *SD* = 48.6).

Relationships Between Momentary Distress and Motor State

Figure 1 is a mean error bar graph that plots Motor against person-mean centered episodic distress. Episodic distress was person-mean centered to calibrate participants' ratings relative to the individual. A visual inspection of Figure 1 indicates participants experienced greater levels of episodic distress when they were off and off-coming-on compared to when they were on and on-wearing-off. Greater levels of episodic distress during off periods compared to on periods aligns with the findings of earlier studies. The apparent difference in levels of episodic distress between transitional motor states (i.e., off-coming-on versus on-wearing-off) is a new finding.

The first GLMM (Model 1) comprised of five fixed effects (Motor, Company, Medication, Trigger, and Time) and two random effects (comprising of an intercept and a slope). The random intercept was defined using an index variable that identified each

participant (ID) and modelled variation in episodic distress between them. The random slope represented the relationship between ID and Time for each participant separately. Overall, Motor and Time were the only significant predictor fixed effects of episodic distress (see Table 3) and this model correctly classified 62.2% of responses. The parameter estimates for the four nominal motor states show that on periods and on-wearing-off states were associated with significantly less episodic distress than off periods (see Supplementary Material 2). However, there was no significant difference in episodic distress when off and off-coming-on, aligning with a visual inspection of Figure 1.

The significant Time fixed effect indicated that (overall) participants were more distressed as each day progressed. The parameter estimates for the random slope (see Supplementary Material 2) suggested that this change in episodic distress over the course of a day did not significantly vary between participants. However, the parameter estimates for the random intercept found significant variation in the spread of episodic distress between participants, ID: Estimate = 0.927, *SE* = 0.423, *Z* = 2.192, *p* = .028, 95% *CI* [0.379, 2.266]. This suggested the pattern of increasing episodic distress as a day progressed was generalizable to the sample and did not differ between individuals, despite variation in the spread of episodic distress between participants.

Relationship Between Episodic Distress, Momentary Cognitive Attentional Syndrome Activation, And Metacognitions

According to the S-REF model, rumination, symptom focus, and worry are all components of a CAS. The raw data of this study generated three separate variables to represent these cognitive processes. If these three variables represented a single, latent-variable, a composite CAS score could be calculated. Specifying a single CAS variable, rather than three variables representing separate cognitive processes, would reduce the number of parameters needed to be estimated for the GLMM. To justify the creation of a

single CAS variable, a principle components analysis of the entire dataset was conducted. This revealed that the three survey items referring cognitive processes loaded heavily on a single factor (factor loadings: rumination = 0.91; symptom focus = 0.92; and worry = 0.88). This factor had an Eigen value of 2.44 that explained 81.4% of the variance. This latent variable was labelled CAS and calculated by summing rumination, symptom focus, and worry responses. The CAS variable was person-mean centered because (1) it was time-dependent and (2) this would represent within-participant differences (i.e., how individuals rate their engagement in momentary rumination, symptom focus, and worry on a five-point, Likert-type scale was assumed to be personally, rather than generally, calibrated). PM and NM scores were grand-mean centered to create variables representing between-participant differences.

Figure 2 displays four spaghetti plots of CAS against person-mean centered episodic distress paneled by momentary motor state. The thickest line in each of the four plots represents the relationship between individually-relative, momentary CAS activation and episodic distress across all participants. A visual inspection of these spaghetti plots suggests a positive relationship between momentary CAS activation and episodic distress that appears more pronounced during off and on periods than transitional motor states. However, the slope in the on-wearing-off panel appears steeper than that in the off-coming-on panel. This suggests that CAS activation influences episodic distress more when participants were wearing off than when coming on.

The significant fixed effects from Model 1 (Motor and Time) were specified in the second GLMM (Model 2) along with three new fixed effects (CAS, PM, and NM). The same random effects specified in Model 1 were used in this model. Model 2 found that the overall effect of Motor, Time, CAS, and NM (but not PM) were significant predictors of Distress (see Table 3). Higher Distress was associated with higher CAS and baseline NM scores. The

addition of CAS, PM, and NM altered the relationships between the transitional motor states and off periods compared to Model 1: i.e., there were no longer significant differences between them (see Supplementary Material 2). Like Model 1, the random intercept but not the random slope was a significant predictor of episodic distress (see Supplementary Material 2), ID: Estimate = 1.344, *SE* = 0.521, *Z* = 2.560, *p* = .010, 95% *CI* [0.620, 2.869]. Model 2 correctly classified 70.0% of responses.

Feasibility of Ecological Momentary Assessment

The usability survey indicated only one participant reported that using the App during both on and off periods was 'quite hard', the rest said it was either 'very easy' (on periods = 15; off periods = 12) or 'quite easy' (on periods = 4; off periods = 7). Of those who did not find it 'very easy' to use the App, the most common feedback was a request to increase the font size of survey items. The majority of participants (*n* = 11) described feeling 'nothing' when a random alert sounded and while six said they felt 'pleased or interested'. However, three participants reported they were 'occasionally irritated' (*n* = 2) or 'often irritated' (*n* = 1). Most participants (*n* = 12) stated the number of random alerts per day was 'about right' and six said they would have been happy with more (though two reported there were too many). Just over half the participants (*n* = 11) said the 1-week length of the study was 'about right'. Seven stated they would have been happy to take part in the study for 2 to 3 weeks, but two said the 1-week duration of the current study was 'too long'. Nineteen participants said the ability to dismiss or postpone random alerts was either 'very helpful' (*n* = 11) or 'somewhat helpful' (*n* = 8), while one stated it was 'neither helpful nor unhelpful'. All participants stated they would 'definitely' or 'possibly' have liked some feedback on their App responses at the end of each day. The most common suggestion for feedback was an illustration of their daily mood changes.

Discussion

This study generated longitudinal data in a naturalistic setting, employing EMA delivered via touchscreen smartphones in a sample of people living with PD, and had two central objectives. It aimed to assess the acceptability and feasibility of using smartphone devices to collect EMA data in a sample of people living with PD who had developed motor fluctuations and to identify predictors of episodic distress. The latter was operationalized and tested by two hypotheses: (1) there would be a relationship between momentary motor state and episodic distress, and (2) cognitive processes and metacognitions would significantly predict episodic distress when controlling for motor state.

EMA was judged acceptable to nearly all the participants and seven said they would be prepared to participate in a study of a longer duration. However, one individual was initially enrolled in the study but later decided to not participate after reflecting on the EMA study demands (this individual did not contribute data to the current study). None of the participants reported the App was substantially more difficult to use across motor states (the participant who reported that it was 'quite hard' to use the App gave the same rating for both on and off periods). This suggests that the usability of the App was independent from motor state, and difficulty-of-use was the result of individual differences (e.g., some individuals may not be comfortable using touchscreen devices). The usability of EMA could be improved by presenting items in a larger font. Combined with the evidence on data completeness, the present study support a previous research (Broen et al., 2016) on the feasibility of using EMA with a mobile device in PD.

Episodic distress seemed to worsen as the day progressed in this sample in contrast to the diurnal increase in positive affect found in depressed individuals in the general population (Peeters, Berkhof, Delespaul, Rottenberg, & Nicolson, 2006). It is possible that the EMA methodology itself contributed to this finding: e.g., perhaps participants became increasingly distressed as the day progressed as they waited for an alert to complete yet another survey.

Another possible explanation is that participants were more distressed as the day progressed because of increasing fatigue and/or a cumulative effect of dealing with symptoms.

The current study also investigated the effect of the time elapsed since the most recent DRT dose and episodic distress. Contrary to Maricle et al.'s (1995), the current study did not find a significant relationship between these variables. Additionally, the current study did not find a significant relationship between episodic distress and psychosocial context: i.e., the presence or absence of other people was not associated with episodic distress when controlling for momentary motor state.

Overall, the results provide further evidence for a relationship between episodic distress and momentary motor state (hypothesis 1): i.e., episodic distress is worse during off periods compared to on periods. However, a counterintuitive pattern was observed for the transitional motor states: i.e., greater episodic distress was reported when participants were off-coming-on compared to when they were on-wearing-off (see Figure 1). It might be assumed that wearing off would be associated with greater episodic distress because this signifies the onset of worsening motor symptoms. Possibly, when individuals are waiting to come on, they might engage in increased symptom focus (part of the CAS, which this study found was associated with episodic distress) to monitor for any improvement because of concerns about delayed on and no effect DRT dose-responses. Whereas, once wearing off has been identified, the focus is more on practical coping strategies (e.g., taking medication). Some support for this interpretation is offered by the spaghetti plots (Figure 2), which suggests that CAS activation has little relationship to episodic distress when on-wearing-off compared to off-coming-on. While the pattern relative to on and off periods may reflect interactions between motor and non-motor factors, the results may also reflect limited power to separate out subtle differences in motor state and/or reliability of self-report. This study also offers partial support for the second hypothesis: i.e., episodic distress is greater at times

when a person is engaging in the CAS and generally higher in those individuals holding negative metacognitive beliefs about symptom control (independently of motor state). The significance of the CAS and negative metacognitions in predicting episodic distress align with an earlier model suggested by Brown and Fernie's (2015), although their hypothesized role of positive metacognitions was not supported by the present data.

These present results suggest novel potential targets for a non-pharmacological intervention aiming to reduce motor fluctuation-related distress in PD. Metacognitive Therapy (MCT; Wells, 2009), based on the S-REF model, is relatively new psychological approach. Unlike CBT, which directly aims to modify the content of maladaptive thoughts and beliefs, MCT aims to weaken perseverative CAS configurations. In light of the current study's findings, which suggest that CAS configurations play an importantly role in episodic distress in PD, future research should investigate the effect of MCT interventions in this population. A variety of relatively simple tools and techniques are used in MCT that can be practiced by the individual in their own time such as Attention Training Technique, which aims to improve attentional control and disrupt perseverative CAS configurations (Wells, 1990). Additionally, MCT interventions could be used to modify NM found by the current study to be associated with episodic distress.

Limitations

This study is subject to several limitations. Firstly, the study's sample size was relatively small for an EMA study, although not unusually so for one conducted in a clinical population (see aan het Rot, Hogenelst, & Schoevers, 2012 for a review). Secondly, only 50.2% of random alerts in this study resulted in a complete EMA survey, whereas Broen et al (2016) reported a substantially higher rate of compliance (84%, range 76% to 96%; $n = 5$) with a more demanding schedule (i.e., ten alerts per day). In the current study, surveys could be dismissed and self-triggered - an option incorporated following consultation with an

expert patient group. Although, the incorporation of self-triggered survey data raises concerns about response biases (e.g., participants might systematically initiate and complete surveys when feeling less distressed), the results did not support this contention (i.e., how surveys were triggered was not significantly associated with episodic distress). Thirdly, five participants did not complete any EMA surveys when they were in an off state, restricting the range of data they contributed to the GLMMs. Fourthly, assessment of momentary motor state was reliant on a self-report survey item. Future studies could consider using accelerometer data from smartphones and/or wearable devices to triangulate self-reports of momentary motor state. Fifthly, the design of the current study did not control for the impact that off periods have on cognitive functioning (see Goldman et al., 2018), which may have amplified measurement error in survey responses (assessing levels of episodic distress and CAS activation) in such motor states. Future studies might consider evaluating participants' cognitive functioning with neuropsychological testing during on and off states before beginning EMA study. These measurements could help to build GLMMs to control for variation in EMA responses due to different levels of cognitive impairment in on and off states. Sixthly, the sample was not specifically selected for the presence of motor fluctuation-related distress This was intended to assess a range of motor fluctuation-related psychological change. It is possible that different patterns of results may emerge in a high distress sample. However, although the final models may change, it is judged likely that similar factors would be identified. Finally, PAS and PHQ-9 scores were controlled for in the GLMMs. However, finding either of these variables to be episodic distress would not have revealed novel targets for psychological intervention.

Conclusions

Despite these limitations, the current study provides evidence for the expected relationship between motor state and episodic distress using longitudinal, naturalistic real-

time data. It also indicates a significant contribution of non-affective psychological factors in determining the severity of episodic distress in people living with PD who experience motor fluctuations. The results suggest the potential clinical value of applying techniques from MCT that aim to reduce perseverative CAS configurations. This study also supports Broen et al.'s (2016) conclusion that EMA is a feasible tool for PD research.

Documentation of Author Roles

Role codes

1. Research project: A. Conception, B. Organization, C. Execution.

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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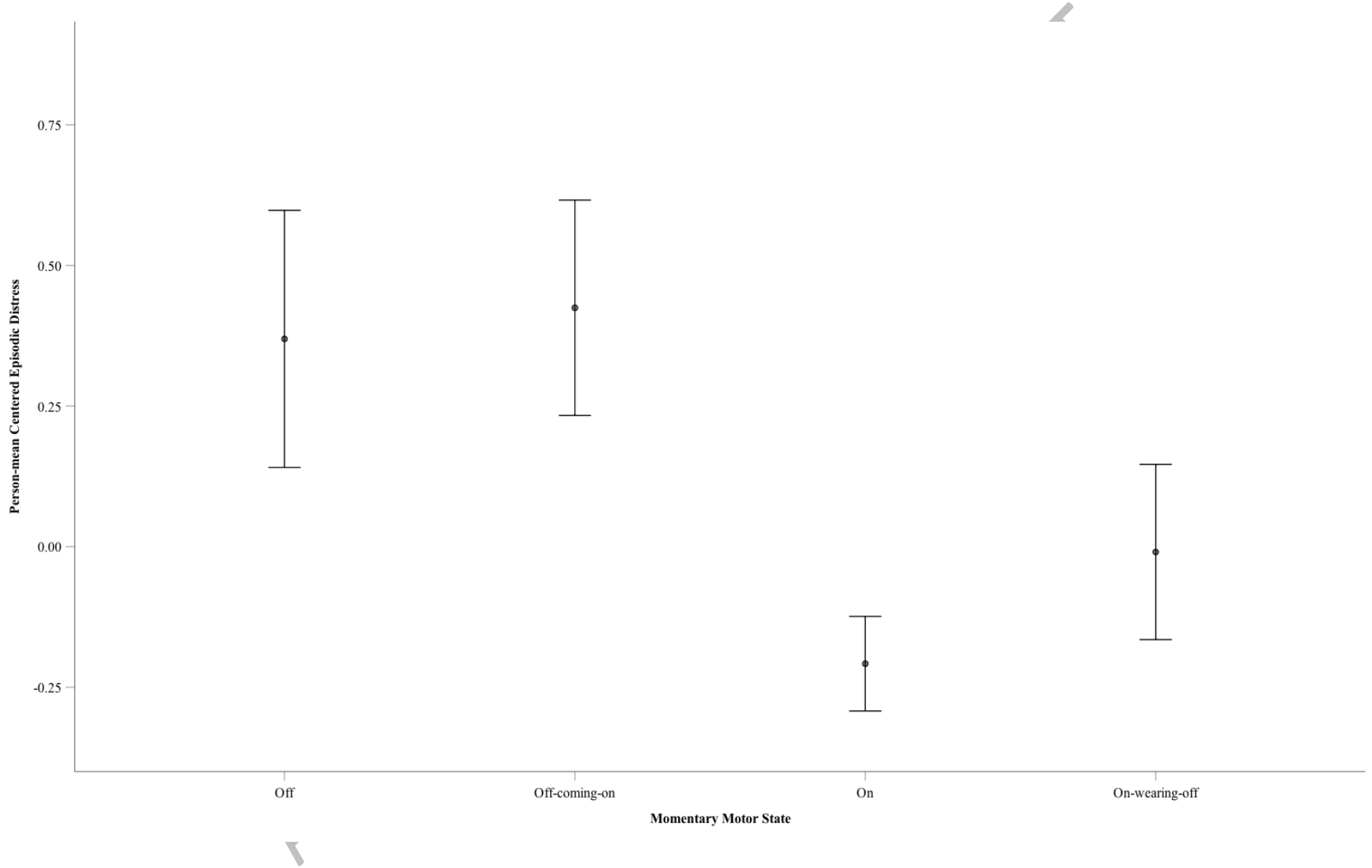
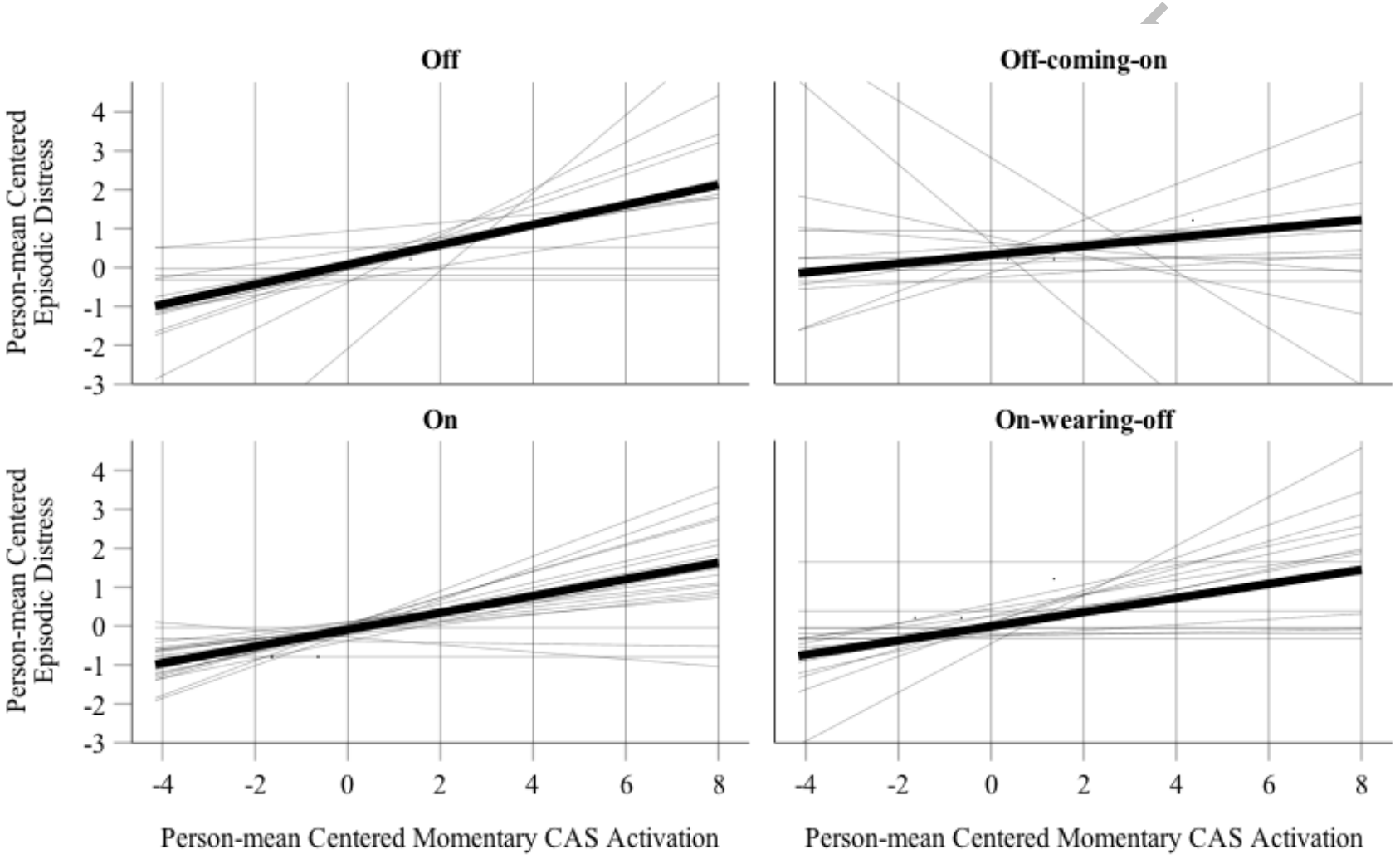
Figure 1: *Mean Error Bar Graphs of Episodic Distress by Momentary Motor State*



Notes. Error Bars = 95% Confidence Intervals; data-points = 498; *n* = 20.

Figure 2: *Spaghetti Plots of Momentary CAS Activation by Episodic Distress Panelled by Motor State*



Notes. Thin lines = lines of best for each participant; thick lines = lines of best fit combining data from all participants; data-points = 498; n = 20.

Table 1: *Means, Standard Deviations, Ranges, and Correlations of Self-Report Measures*

Measure	Mean	*SD*	Range	1	2	3	4	5	6	7
1. MaSCS – PM	20.78	5.79	9-29		.02	.37	-.18	-.09	-.02	-.15
2. MaSCS – NN	18.05	5.34	8-32			.38	.40	.40	.49*	.54*
3. PAS – Avoidance	4.15	2.64	0-9				.37	.52*	.70**	.50*
4. PAS – Episodic	3.55	3.68	0-16					.65**	.75**	.52*
5. PAS – Persistent	9.05	5.40	2-20						.93**	.51*
6. PAS – Total	16.75	9.88	2-42							.67**
7. PHQ-9	11.15	5.10	2-22							

Note. MaSCS = Metacognitions about Symptom Control Scale (PM = positive metacognitions; NM = negative metacognitions); PAS = Parkinson's Anxiety Scale; PHQ-9 = Patient Health Questionnaire - 9; * $p < 0.05$; ** $p < 0.01$; $n = 20$.

Table 2: *Trigger and Momentary Motor State of Completed Surveys*

	Random alerts		Participant-initiated		Total	
	Count (% of motor state)	Median (IQR) and range	Count (% of motor state)	Median (IQR) and range	Count (% of completed surveys)	Median (IQR) and range
Completed surveys						
Over study period	281	15.5 (8.5); 1 to 24	217	7 (11); 1 to 28	498	26 (12.25); 8 to 38
While off	43 (51.8%)	1.5 (4); 0 to 8	40 (48.2%)	1 (3); 0 to 7	83 (16.7%)	3 (5.5); 0 to 15
While off-coming-on	33 (54.1%)	1 (2.5); 0 to 7	28 (45.9%)	1 (2); 0 to 6	61 (12.2%)	3 (2.5); 0 to 8
While on	153 (57.1%)	7 (6.5); 0 to 16	115 (42.9%)	3 (4.5); 0 to 20	268 (53.8%)	12 (9); 4 to 32
While on-wearing-off	52 (60.5%)	3 (4.25); 0 to 6	34 (39.5%)	1 (2); 0 to 10	86 (12.2%)	3 (2.5); 0 to 8

Note. Study period = 7 days; $n = 20$.

Table 3: *Fixed Effects for Two Generalised Linear Mixed Models with Episodic Distress as The Dependent Variable*

Fixed effect	Model 1: F (df_1, df_2)	Model 2: F (df_1, df_2)
Corrected model	35.47 (9, 489) ***	23.68 (7, 483) *
Motor	14.53 (3, 489) ***	10.40 (3, 483) ***
Time	8.68 (1, 35) **	12.42 (1, 23) **
Company	1.40 (3, 489)	-
Medication	1.14 (1, 489)	-
Trigger	0.09 (1, 489)	-
CAS	-	41.14 (1, 483) ***
PM	-	0.50 (1, 10)
NM	-	7.21 (1, 6) *

Note. Motor = motor state; Time = person-mean centred hour of day; Company = psychosocial context; Medication = interval between present moment and last dopamine replacement therapy; Trigger = how a survey initiated; CAS = person-mean centred Cognitive Attentional Syndrome; PM = positive metacognitions; NM = negative metacognitions; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; $n = 20$.

Supplementary Material 1: *Ecological Momentary Assessment Survey Items*

Construct (variable name)	Item	Responses	Recoding (data-type; levels)
Motor state (Motor)	"At the moment I am…"	(0) "on"; (1) "on-coming-off"; (2) "off-wearing-on"; (3) "off" *	No recoding (categorical; four-level)
Psychosocial context (Company)	"Who is with you?"	(0) "no-one"; (1) "people I don't know"; (2) "friends or family"; (3) "other people I know" *	No recoding (categorical; four-level)
Time elapsed since last DRT dose (Medication)	"I took my last tablet…"	(0) "more than an hour ago"; (1) "31-60 minutes ago"; (2) "less than half an hour ago"	(0) more than an hour ago; (1) one hour or less* (categorical; two-level)
Rumination (CAS)	"Were you dwelling on your thoughts, feelings, and/or physical symptoms?"	Five-point Likert-type scale; (0) "not at all" to (4) "extremely"*	Component variables summed to create a composite CAS score (ordinal; five-level)
Symptom focus (CAS)	"Were you focusing on your symptoms?"		
Worry (CAS)	"Were you worrying about things?"		
Episodic distress (Distress)	"Were you feeling distressed?"		No recoding (ordinal; five-level)

Notes. CAS = Cognitive Attentional Syndrome; DRT= dopamine replacement therapy. * = reference category.

Supplementary Material 2: *Parameter Estimates for Two Generalised Linear Mixed Models with Episodic Distress as The Dependent Variable*

Fixed effects		Estimate	*SE*	*t*	*p*	CI_{95} Lower	CI_{95} Upper
	Model 1						
Motor	**On period**	**-1.037**	**.2059**	**-5.034**	**.000**	**-1.441**	**-.632**
	On-wearing-off state	**-.456**	**.1699**	**-2.682**	**.008**	**-.789**	**-.122**
	Off-coming-on state	.061	.2190	.277	.782	-.370	.491
	Off period [RC]	0	.	.	.	.	.
Time		**.051**	**.0175**	**2.946**	**.006**	**.016**	**.087**
Company	No-one	.041	.1738	.236	.813	-.300	.383
	People I don't know	1.018	.5638	1.805	.072	-.090	2.126
	Friends and family	.240	.1978	1.215	.225	-.148	.629
	Other people I know [RC]	0	.	.	.	.	.
Medication	More than an hour ago	-.143	.1343	-1.065	.287	-.407	.121
	1 hour ago, or less [RC]	0	.	.	.	.	.
Trigger	Random alert	.039	.1293	.305	.760	-.215	.293
	Participant initiated [RC]	0	.	.	.	.	.
	Model 2						
Motor	**On period**	**-.474**	**.1964**	**-2.413**	**.016**	**-.860**	**-.088**
	On-wearing-off state	-.129	.2054	-.631	.529	-.533	.274
	Off-coming-on state	.277	.1815	1.527	.127	-.079	.634

Off period [RC]	0	.	.	.	.	.
Time	**.053**	**.0150**	**3.524**	**.002**	**.022**	**.084**
CAS	**.311**	**.0485**	**6.414**	**.000**	**.216**	**.407**
Positive Metacognitions	-.030	.0429	-.699	.501	-.126	.066
Negative Metacognitions	**.110**	**.0410**	**2.685**	**.037**	**.009**	**.211**

Random effects	Estimate	*SE*	*Wald Z*	*p*	CI_{95} Lower	CI_{95} Upper
Model 1						
Intercept (ID)	**.927**	**.423**	**2.192**	**.028**	**.379**	**2.266**
Slope (ID by Time)	.002	.001	1.227	.220	.000	.008
Model 2						
Intercept (ID)	**1.334**	**.521**	**2.560**	**.010**	**.620**	**2.869**
Slope (ID by Time)	6.325×10^{-5}	.001	.068	.946	2.170×10^{-17}	1.843×10^{6}

Note. RC = reference category; Motor = motor state; Time = person-mean centred hour of day; Company = psychosocial context; Medication = interval between present moment and last dopamine replacement therapy; Trigger = how a survey initiated; CAS = person-mean centred Cognitive Attentional Syndrome; ID = participant identifier; bold type indicates variable or variable level with a significant *p*-value; $n = 20$.